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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,710	12/22/2004	Hideki Matsui	MATSUI9	9993

1444 7590 06/27/2006

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EXAMINER	
BRADLEY, CHRISTINA	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 06/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/518,710	MATSUI ET AL.	
	Examiner	Art Unit	
	Christina Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *22 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

1. Claims 1-4 are objected to because of the following informalities: in claim 1, calcineurin is written "calcineulin". Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

4. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

5. Claims 1-4 are drawn to inhibitors of calcineurin subunit A cleavage by calpain comprising SEQ ID NO: 1, SEQ ID NO:2 and/or analogues thereof. Analogues of SEQ ID NOs: 1 and 2 include peptides with deletions, substitutions, insertions and additions at the termini as

well as fusions to other compounds. The specification discloses only the following complete or partial structures of such inhibitors: SEQ ID NOs: 1 and 2 and SEQ ID NOs: 5 and 6 which comprise SEQ ID NOs: 1 and 2, respectively, and a leader sequence to facilitate cellular uptake. The specification does not provide information on the physical or chemical properties that are essential for inhibition, or guidance on how to obtain specific analogues that meet the functional limitations of the claimed inventions. The specification does not present a correlation between the structure (i.e. identity of amino acids at specific positions in the peptide) and the function of inhibiting calpain. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

6. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

7. With the exception of SEQ ID NOs: 1, 2, 5 and 6, the skilled artisan cannot envision the detailed chemical structure of the calpain inhibitor. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required.

See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

8. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

9. Therefore, only SEQ ID NOs: 1, 2, 5 and 6, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

10. Claims 1, 2 and 4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NOs: 1, 2, 5 and 6, does not reasonably provide enablement for all other calpain inhibitors comprising SEQ ID NOs: 1 and 2 and/or their analogues. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

11. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

12. The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) the nature of the invention

13. The invention is drawn to inhibitors of calcineurin subunit A cleavage by calpain comprising SEQ ID NO: 1, SEQ ID NO:2 and/or analogues thereof. The compounds are designed to be suppressants of neuronal cell death (claim 2) and progress of a disease associated with dementia (claim 3).

(2) the state of the prior art

14. Calpain inhibitors are known in the art (see User Protocol for the Calpain Inhibitor Set from Calibochem). However, these compounds differ in their chemical structures from those of the instant application. Structural details on calpain activity and regulation have been obtained by high-resolution x-ray crystallography (see Hosfield *et al. EMBO J.*, **1999**, *18*, 6880).

(3) the relative skill of those in the art

15. The relative skill of those in the art is high.

(4) the predictability or unpredictability of the art

16. An enormous number of peptides are encompassed in the scope of the instant application. Experimental information on the structure and activity of each of these species is not available either in the specification or the prior art. Thus, lacking experimental data, the skilled artisan is left to predict which analogues of SEQ ID NOs: 1 or 2 would be effective in the claimed application. The ability to predict whether or not a particular analogue of SEQ ID NOs: 1 or 2 is active depends on the ability to predict the structure of the peptide, and the ability to predict the interaction of the peptide and calpain.

17. Regarding structure prediction, the state of the art, though advanced in recent years, is not at a level to provide the detailed atomic- resolution information necessary to predict ligand-receptor interactions. In their recent review of the field Ginalski *et al.* (*Nuc. Ac. Res.*, **2005**, *33*, 1874) write: "Unfortunately, the protein structure prediction field is currently unsuccessful in keeping its promise of making the drug development process much more efficient. Predicted protein structures can be used if very close homologs with known structure are available, but in most cases rational drug design requires iterative co-crystallization of the protein-ligand complexes. In the majority of cases, predicted models are of insufficient quality to offer atomic details necessary for lead optimization. Currently available structure prediction methods do not allow for high-quality predictions of the quaternary structure of protein complexes and for the prediction of interactions between proteins. Current benchmarks indicate that methods predicting interactions can be successful mainly in case when structures exhibit minimal conformational changes upon complex formation. Substantial errors observed n predicted models go beyond the limits tolerated by such methods."

18. Even when a protein structure is known and its activity well-established, it is difficult to predict the effect of individual amino acid substitutions or deletions. Rudinger (Peptide Hormones (Ed. J.A. Parson). University Park Press. Baltimore, 1976, pp. 1-7) states: "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study." Recent examples in the art suggest that Rudinger's assessment of the unpredictability of amino acid substitution effects is still valid. Pitt *et al.* (*Nuc. Ac. Res.*, **2000**, *28*, 4419) report that random mutagenesis of the σ^{54} RNA polymerase uncovered five independent single amino acid substitutions that lead to defective transcription. Bradley *et al.* (*J. Mol. Biol.*, **2002**, *324,* 373) demonstrate that an Ala -> Gly substitution in six analogous structural environments of an ankyrin repeat protein have remarkably diverse effects on protein stability. Flanagan *et al.* (*Proc. Natl. Acad. Sci. USA*, **1992**, *89*, 748) show that the deletion of thirteen amino acids from the C-terminus of the 149-residue staphylococcal nuclease results in a loss of 50% of the helicity but does not cause the protein to unfold into a disordered chain. A dramatic example of the effect of single amino acid substitutions is in sickle cell anemia. This disease, characterized by chronic haemolysis and susceptibility to infection, is caused by a single Glu -> Val substitution in the β-globin gene (Schnog *et al. J. Med.*, **2004**, *62*, 364). Finally, Sawai *et al.* (*Prot. Engin.*, **2002**, *15*, 225) show that this lack of predictability extends to short peptides as well: specific single amino acid substitutions in an eighteen-residue antimicrobial peptide dramatically reduce toxicity and affect the structure of the peptide in subtle ways.

19. Clearly the state of the field is such that even the skilled artisan can not predict the effect of amino acid substitutions and deletions on the activity of SEQ ID NOs: 1 or 2, especially for the new application of treating dementia.

(5) the breadth of the claims

20. Claims 1-4 are drawn to inhibitors of calcineurin subunit A cleavage by calpain comprising SEQ ID NO: 1, SEQ ID NO:2 and/or analogues thereof. Analogues of SEQ ID NOs: 1 and 2 include peptides with deletions, substitutions, insertions and additions at the termini as well as fusions to other compounds.

(6) the amount of direction or guidance presented; (7) the presence or absence of working examples

21. Despite the lack of predictability, the specification provides only limited working examples: *in vitro* inhibition of calcineurin cleavage and a reduction in neuronal cell death in response to the administration of SEQ ID NOs: 5 and 6. This level of guidance is insufficient to permit the skilled artisan to use the invention within the full scope of claims 1, 2 and 4 because it fails to identify the structural features that are necessary for the observed function. Accordingly, it is not possible for the skilled artisan to easily identify other analogues that would exhibit the claimed activity. With respect to claim 3, in the absence of *in vivo* data it is not possible to judge the effectiveness of any of the claimed compounds for the suppression of a progress of a disease associated with dementia.

(8) the quantity of experimentation necessary

22. Considering the factors above, the skilled artisan would be burdened with undue experimentation in determining if an analogue of SEQ ID NOs: 1 or 2 would be effective at

inhibiting calpain or suppressing neuronal cell death or suppressing the progress of a disease associated with dementia. Each would require performing *in vitro* calpain inhibition assays, assays for the inhibition of calcineurin cleavage and assays for the suppression of neuronal cell death with a broad range of the claimed compounds. The latter application would be particularly burdensome and would require the development of *in vivo* assays and/or animal models for a wide range of disease characterized by dementia to test the efficacy of the claimed compounds.

23. Thus, with regard to claims 1, 2 and 4, the specification while enabling for the use of SEQ ID NOs: 1, 2, 5 and 6, is not enabling for the use of all other analogues of SEQ ID NOs: 1 and 2. The specification is not enabling for the use of the invention of claim 3 in its entirety.

Conclusion

24. No claims are allowed.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Bradley whose telephone number is (571) 272-9044. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M.

26. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

27. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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